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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,703	10/31/2003	H. William Bosch	029318-0973	8369

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EXAMINER	
MAHYERA, TRISTAN J	

ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,703	BOSCH ET AL.	
	Examiner	Art Unit	
	TRISTAN J. MAHYERA	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-31,36-38,40 and 44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31,36-38,40 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/27/2008, 10/8/2008, 10/29/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/27/2008 has been entered.

Response to Arguments and Amendments

The declaration filed on 8/22/2008 under 37 CFR 1.131 is sufficient to antedate the OLIVERI reference. Applicants' further arguments are moot in light of the new rejections.

Claim Rejections - 35 USC § 112

The rejection of Claims 19 and 21is **withdrawn** in light of Applicants' amendments.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Examiner has considered the factual inquires set forth in *Graham* **v.** *John Deere Co.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-15 and 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over REINER et al (US 5,711,961) in view of RYDE et al. (US 6,375,986).

REINER teaches gum tablets containing microgranules (i.e. particles) with an active adsorbed onto the surface. See e.g. abstract and claim 1. The active is exemplified in Example 11 where a 1.55g tablet contains 50g of nimesulide. This tablet

also contains surface stabilizers, specifically two or more surface stabilizers such as glycerol, HPMC and polyethylene glycol. See e.g. Example 11: instant clam 9. The dosage is taught to be an oral tablet with immediate release and slow release characteristics. See e.g. col. 5 lines 54-60: instant claims 4 and 5. The tablet is believed to have bioadhesive qualities because the nimesulide is adsorbed on the particle: Instant claim 15. The particle size is about 850 micron which is larger than the 2000 nm of the instant invention.

REINER does not teach nanoparticles of less than 2000nm or other stabilizers.

RYDE teaches compositions of solid nanoparticles having an active, at least one polymeric surface stabilizer and DOSS whereby upon administration to a human the composition exhibits dramatic redispersion of the nanoparticles. See e.g. col. 5 lines 16-23 and lines 55-67. The high redispersibility is not limited to a specific drug or drug class, however, it is limited to nanoparticulate compositions comprising at least one polymeric surface stabilizer and DOSS. See e.g. col. 6 lines 12-19. The nanoparticles that best achieve this redispersion quality can be less than 200nm. See e.g. Example 3 with sizes of 100nm reading on instant claims 1-31, 36-38, 40 and 44. Polymeric surface stabilizers physically adhere to the surface of the nanoparticulate active agent, but do not chemically react with the drug or itself, which reads on the adsorbtion of the instant invention. See e.g. col 7 lines 27-31. Exemplified stabilizers are HPMC, polysaccharides and PLASDONE s-630, a cationic random copolymer of vinyl pyrrolidone and vinyl acetate in a 60:40 ratio (NVP/VA). See e.g. col 7 lines 40, 42 and 47-48, Example 3: instant claims 1, 6-14. The active is present from 99.8% to about

0.1%, which reads on the instant claim 7. See e.g. claim 2. The stabilizer is present from about 0.01% to about 90%, which reads on instant claim 8. See e.g. claim 5. The active is selected from a crystalline, semi-crystalline or amorphous phases: instant claim 2. See e.g. claim 13.

Instant Claims 1, 3, 27-31 are directed to an effective particle size of nimesulide or additional nimesulide composition. Claim 1, 28 and 30 state "less than about 2000nm"; Claim 3, 29, 31 state "less than 1900nm"; Claim 27 states a different size than the nimesulide composition of Claim 1. RYDE describes a particle size as "small" when it is below 1 micron and Example 3 exemplifies sizes of 100nm, which read on these claims. See e.g. Example 3.

Instant Claims 4–6 are directed to oral administration of the composition and tablets as the dosage form and further excipients or carriers. RYDE describes preparation of the desired oral pharmaceutical form, specifically a tablet. See e.g. col. 5 lines 47-48.

Instant Claims 7-14 are directed to at least one surface stabilizer. RYDE describes numerous actives that can be present with the stabilizer NVP/VA and the further combination with non-nimesulide agents and additional excipients, stabilizers or carriers. See e.g. claim 14 and Example 3.

Claims 1 10-13 and 15-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of LIVERSIDGE et al. (US 5,552,160 see PTO-1449 filed 4/01/2004).

REINER and RYDE teach compositions of solid nanoparticles having nimesulide, at least one polymeric surface stabilizer and DOSS whereby upon administration to a human the composition exhibits dramatic redispersion of the nanoparticles, as described above.

REINER and RYDE do not exemplify any Tmax, Cmax or AUC profile of nimesulide.

LIVERSIDGE teaches that nanoparticles of NSAIDs having a surface modifier adsorbed on the surface hasten onset of the active. See e.g. col 1 lines 61-64. The reference teaches nanoparticles have decreased Tmax, increased Cmax and increased AUC when compared to non-nanoparticles. See e.g. col 9 lines 1-20; instant claims 16-21 and 25-26. The size of the control was between 20-30 microns (see col 7 lines 35-38) while the size of the nanoparticles was between 240-300nm (see col 7 lines 32-34); instant claims 16-21 and 25-26. The composition is considered bioadhesive because the surface modifiers physically adhere to the surface of the NSAID but do not chemically bond to the NSAID. See e.g. col 3 lines 25-27; instant claim 15. LIVERSIDGE further teaches a simple screening process to determine compatible surface modifies with NSAIDs and also the amounts of surface modifier and NSAID can be adjusted by known variables. See e.g. col 6 lines 16-55 and col 6 lines 5-15. It would have been obvious to a person of ordinary skill in the art at the time the invention was made to make a composition comprising nanoparticles of nimesulide and a surface stabilizer that decreases the Tmax and increases the Cmax and AUC of nimesulide compared to non-nanoparticles, as taught by REINER and RYDE in view of

LIVERSIDGE. One of ordinary skill in the art at the time the invention was made would have been motivated to combine these elements into a single composition because of the beneficial effects of hastening the onset of the NSAID, improving dissolution and reducing side effects, as taught by LIVERSIDGE. Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention

Instant Claims 1 and 16-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of SINGH et al. (Analytical Profiles of Drug Substances and Excipients, Volume 28, 2001, p197-249) and in view of BOSCH et al. (US 5,510,118).

Instant Claims 1 and 16-26 are directed to physical properties and pharmacokinetics of nimesulide. REINER and RYDE teach compositions of solid nanoparticles having nimesulide, at least one polymeric surface stabilizer and DOSS whereby upon administration to a human the composition exhibits dramatic redispersion of the nanoparticles, as described above.

REINER and RYDE do not exemplify the Tmax, Cmax and AUC of nimesulide, however, the combination motivates one to improve absorption and bioavailability properties, of which Tmax, Cmax and AUC are indicators.

SINGH et al. describes the pharmacokinetic and bioavailability properties of nimesulide (see section 7) and BOSCH et al. teaches that bioavailability is the degree to which a drug becomes available to the target tissue after administration (see column 1

lines 11-12) and the rate of dissolution of a particular drug can increase with increasing surface area, i.e. decreasing particle size (see column 1 lines 25-27). A person skilled in the art of preparing pharmaceutical compositions would know that decreasing the size of a compound would increase its bioavailability, increase the AUC, increase the Cmax and decrease the Tmax. Claims 16 and 17 are drawn to increased Tmax in nanoparticulate form, Claims 18 and 19 are drawn to an increased Cmax in nanoparticle form, Claims 20 and 21 are drawn to increased AUC in nanoparticle form, and Claims 22-27 are drawn to fed versus fast states and bioequivalence all of which are properties of the composition. Applicants' composition, as claimed, is the same as the prior art. As claimed, Applicants' composition contains the same components in the same configuration as the prior art. Properties are the same when the structure and composition are the same. Thus, burden shifts to applicant to show unexpected results, by declaration or otherwise. *In re Fitzgerald*, 205 USPQ 594. In the alternative, the claimed properties would have been present once the composition was employed in its intended use. *In re Best*, 195 USPQ 433. Thus, it would have been obvious to such a person skilled in the art at the time of the instant invention that the nanoparticle composition containing nimesulide, a stabilizer and DOSS as taught by REINER in view of RYDE would have claimed properties because the compositions of the prior art and the instant are identical and one would understand the relationship between Tmax, Cmax and AUC in light of nimesulide from SINGH in order to improve bioavailability.

Instant Claims 1, 36-38 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of SINGH et al. (Analytical Profiles of Drug Substances and Excipients, Volume 28, 2001, p197-249) and in view of MERCK (The Merck Index 12th ed. Merck & Co. 1996, codeine, p416-417).

Instant Claims 36-38 and 40 are directed to the addition of a non-nimesulide active agent, such as analgesics, specifically codeine. REINER and RYDE teach compositions of solid nanoparticles having nimesulide, at least one polymeric surface stabilizer and DOSS whereby upon administration to a human the composition exhibits dramatic redispersion of the nanoparticles, but do not teach adding additional specific additional analgesics to the composition.

SINGH et al. teaches it is well known in the art that nimesulide has anti-inflammatory and analgesic properties. See section 1.5. It is also well known in the art that codeine has analgesic properties as shown in MERCK. Furthermore, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). Thus, the addition of codeine, an analgesic, would be obvious to someone of skill in the art at the time of the invention because nimesulide also has known analgesic properties, resulting in the practice of the instantly claimed invention with a reasonable expectation of success: instant claims 36-38 and 40.

Instant Claims 1 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over REINER and RYDE in view of BUHL et al. (US 5,776,563 see PTO-892 filed 9/5/2007).

Claim 44 is directed to sterile filtration of the composition of claim 1. REINER and RYDE teach compositions of solid nanoparticles having nimesulide, at least one polymeric surface stabilizer and DOSS whereby upon administration to a human the composition exhibits dramatic redispersion of the nanoparticles, but does not specify a method of sterilization, although it is stated that the composition is administered to humans which implies that some form of sterilization was accomplished.

BUHL teaches that pharmaceutical compositions can be sterilized by conventional sterilization techniques or may be sterile filtered, which although not mentioned would *inter alia* prevent microorganisms from being administered to a patient. See column 4 lines 7-26.

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to make a composition that was sterilized, specifically filtered, as taught by BUHL. One of ordinary skill in the art at the time the invention was made would have been motivated to combine these elements into a single composition because of the beneficial effects of preventing unwanted microorganisms. Absent any evidence to the contrary, and based upon the teachings of the prior art, there would have been a reasonable expectation of success in practicing the instantly claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TRISTAN J. MAHYERA whose telephone number is 571-270-1562. The examiner can normally be reached on Monday through Thursday 9am-7pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, MICHAEL P. WOODWARD can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tristan J Mahyera/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615